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DOI:
10.1016/j.euf.2015.01.001

Document Version
Peer reviewed version

Citation for published version (Harvard):
Bryan, R, Evans, T, Dunn, J, Iqbal, G, Bathers, S, Collins, S, James, N, Catto, J & Wallace, DMA 2015, 'A Comparative Analysis of the Influence of Gender, Pathway Delays, and Risk Factor Exposures on the Long-term Outcomes of Bladder Cancer', *European Urology Focus*, vol. 1, no. 1, pp. 82-9.
https://doi.org/10.1016/j.euf.2015.01.001

A COMPARATIVE ANALYSIS OF GENDER, PATHWAY DELAYS AND RISK FACTOR EXPOSURES ON THE LONG-TERM OUTCOMES FROM BLADDER CANCER

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Disclaimers: All authors have contributed significantly to this manuscript. Professor ND James has previously received honoraria from *Pierre Fabre*. RT Bryan has previously contributed to advisory boards for *Olympus Medical Systems* in relation to narrow band imaging cystoscopy. There are no other disclosures.

Keywords: Urinary bladder neoplasms, delayed diagnosis, sex factors, long term effects, treatment outcome, risk factors.

Word count: Main text 2614 + Abstract 294

Total pages: 28

Tables & Figures: 4 tables + 2 figures.

ABSTRACT

Background: The relationship between pathway delays and bladder cancer-specific survival is complex due to the influence of tumour- and patient-specific factors.

Objective: To investigate the influence of tumour factors, patient factors, carcinogen exposure and pathway delays on the long-term outcome of urothelial bladder cancer (UBC).

Design, Setting and Participants: A cohort of 1537 UBC patients were enrolled 1/1/1991-30/6/1992 and followed-up for 17.7years. The period from onset of symptoms to first treatment (TURBT) was divided into 3 components of potential delay.

Outcome Measurements and Statistical Analysis: Associations between patient factors, tumour factors and delay times were analysed using Pearson's chi-squared test and Mann–Whitney U-test. Survival was calculated from date of TURBT to date of death or censor date of 31/12/2010. Competing risks of death were assessed with the cumulative incidence function (CIF); comparisons of CIFs were performed using Gray's test.

Results: At censor, reliable data were available for 1478 patients, of which 75% had died. Females presented more commonly with muscle-invasive bladder cancer (MIBC) (30% vs. 26%) and less frequently with pT1 disease (18% vs. 24%) (p=0.06), had a longer total delay time (median 120days vs. 106days, p=0.02), and those with MIBC had a significantly higher cumulative incidence of death due to UBC (80% vs. 67% at 17years, p<0.02). Cox regression

identified age, smoking status, and tumour stage, grade, and size as the most significant determinants of poor outcome.

Limitations: We did not capture downstream delays associated with cystectomy or radiotherapy.

Conclusions: Female patients present later than males, and our data suggest that delay in referral may be contributory. The relationship between gender, outcomes, delays and aetiology of UBC is complex.

Patient Summary: We followed a large group of bladder cancer patients for over 17years. The relationship between pathway delays and survival is complex. However, female patients present later than male patients, and our data suggest that delay in referral from general practice may be contributory.

INTRODUCTION

Urothelial bladder cancer (UBC) is the fifth most common cancer in Western societies, accounting for 10,000, 69,000 and 180,000 new cases per year in the UK, USA and EU [1], respectively. The global incidence of the disease is rising reflecting patterns of cigarette smoking and occupational carcinogen exposure [2], the most common aetiological factors [1]. There has been little improvement in the outcome for UBC patients since the 1980s, reflecting complex diagnostic pathways and treatment regimens, and a lack of therapeutic advances [3]. Given these constraints, much attention has been paid to reducing delays in presentation [4], diagnosis and treatment [5].

For UBC the relationship between time to diagnosis and treatment, and disease-specific survival is complex [6-9]; many tumours are indolent, for which delay in diagnosis does not alter survival [10], and outcomes from aggressive UBCs are multifactorial [6-9]. In addition to delays in healthcare pathways, disease biology (reflected by stage, grade and tumour characteristics [11;12]) and patient-specific factors are important. The latter reflect aetiological agent exposures (e.g. smoking is more common in males) [9;13;14], gender-specific misdiagnoses (e.g. females are more likely to be incorrectly diagnosed with infection [15]) [1;16;17], and potential differences in the molecular pathogenesis of male and female UBC [18].

To obtain a clearer understanding of factors affecting outcomes in UBC, we have followed a large cohort of prospectively recruited patients since 1991 [9]. This population represents 85% of new cases of UBC arising over an 18month period within the West Midlands region

of the UK [9]. Here we report long-term outcomes and investigate the influence of gender, carcinogen exposure and pathway delays in this cohort.

PATIENTS AND METHODS

Patients

Patients newly-diagnosed with UBC within the West Midlands (UK) were prospectively recruited from 1st January 1991 through 30th June 1992 [9]. Data regarding exposures, dates of onset of symptoms, first referral by GP, first hospital appointment and first treatment (date of TURBT) were collected at recruitment. Data were checked to ensure that TNM classification correlated with histopathology and bimanual examination findings. Discrepancies were resolved by the investigators and the operating Consultant. All patients were notified to the West Midlands' cancer registry, who provided death information at the censor date of 31st December 2010. Ethics committee approval was received prior to study opening. Ex-smoking was defined as abstinence for >12 months. Occupational exposure was identified by 3 assessors (>90% consensus) utilising IARC contemporary evidence to assign no risk, possible risk and definite risk of working in an occupation implicated in the pathogenesis of UBC (see Supplementary Table 1) [19].

Pathway measures

Pathway times were defined as:

- Time 1: date of onset of patient's symptoms to date of GP's first referral to secondary care;
- Time 2: date of GP's first referral to secondary care to date of first hospital attendance for urological assessment;
- Time 3: date of first hospital attendance to date of first treatment by TURBT.

Hospital delay included the addition of Times 2 and 3, and Total delay was the summation of all three time periods.

Statistical Methods

All statistical analyses were performed using Stata 11.2 (*StataCorp LP, College Station, Texas, USA*) and R version 2.13.2 (*The R Foundation for Statistical Computing, http://www.R-project.org*). Associations between patient and tumour features, with median delay times were analysed using Pearson's chi-squared test for categorical data and the Mann–Whitney U-test for continuous data. Survival was calculated from the date of first TURBT to the date of death or censor date of 31st December 2010, using all-cause mortality. Survival curves for each stage (Ta, T1, T2-4) were constructed using the Kaplan-Meier method and outcomes between groups compared using the log-rank test. We estimated relative survival to calculate the crude probability of death in the general population compared to patients diagnosed with pTa tumours using the user written Stata command strs matched for age at diagnosis, sex and year of diagnosis [20]. The calculated probabilities were based upon the Ederer II method. Survival was compared in terms of demographic and tumour characteristics and delay times. A stratified survival analysis was used to test for differences within delay times adjusting for tumour stage and to test for smoking status adjusting for delay times. Cox-proportional hazards models using a complete case approach were applied to investigate the independent effect of age, sex, smoking status, haematuria, tumour stage, grade, type, size and number. We tested the proportional hazards assumption of the models by examining the Schoenfeld and scaled Schoenfeld residuals; in each test the proportional hazards assumption was met. In addition, we evaluated the fit of the models using Cox-Snell

residuals which confirmed the models to fit the data well. This formed a base model that was used to adjust the effects of each delay. Hazard ratios with 95% CI and P values are presented.

To assess the competing risks of death, we first used a non-parametric test to assess the equality between groups by calculating the cumulative incidence function (CIF) as described by Scrucca et al. [21]. Comparison of specific CIFs was performed using Gray's test [22]. See Supplementary Methods for further details.

RESULTS

Cohort description

In total, 1537 patients were enrolled into the study and reliable long-term survival data were available on 1478 (96.2%) (**Table 1**). The cohort was typical for UBC, with a male to female ratio of 3:1 and a median age at diagnosis of 69 years for male (IQR 62-76) and 71 years for female patients (IQR 64-78). Most patients were current or former cigarette smokers (973, 77%), and 330 (27%) patients were classified as having possible or definite exposure to occupational carcinogens. As detailed previously, patients were treated by contemporaneous standard practice (which did not include re-resection), and surveillance was carried out according to national guidelines [9]. At the censor date, the mean follow-up was 106 months (8.8 years, IQR 22.0-212.8 months) and 1109 patients (75%) had died. The cause of death was known for 983 patients (89% of deaths) (**Table 2**).

Pathological features

There was a significant association between tumour stage and death from UBC (P<0.005, **Figure 1**). Whilst most patients with MIBC died from the disease, the majority of patients with NMIBC died from other causes (**Table 2**); notably, >10% of patients originally presenting with pTa tumours, and >27% of patients originally presenting with pT1 tumours, subsequently died from UBC.

Gender

There was no difference in grade at presentation between the genders (p=0.16). However, females presented more commonly with MIBC (30% vs. 26% for males) and less frequently

with pT1 disease (18% vs. 24% for males) (p=0.06, **Table 3**). Females had a longer total delay time than males (median 120days vs. 106days, respectively, p=0.02) (**Tables 3 and 4**). The majority of this delay arose before hospital referral (**Table 3**); a significantly higher proportion of female patients with visible haematuria encountered a longer delay Time 1 than equivalent male patients (p<0.05, **Table 4**).

Female patients with MIBC had a significantly higher cumulative incidence of death from UBC than male patients at 17 years (80% vs. 67%, p<0.02). There was no difference in UBC mortality between the genders for pTa and pT1 tumours (14% vs. 15%, p=0.56 and 34% vs. 38%, p=0.58, respectively) (**Figure 2a**), and for other causes of death. Female patients with grade 3 tumours had a significantly higher cumulative incidence of UBC death than males (73% vs. 58%, p=0.002), but no difference was seen for grade 1 and 2 (14% vs. 15%, p=0.65 and 32% vs. 38% p=0.23, respectively) (**Figure 2b**).

Cigarette Smoking

At presentation, 77% of patients were current or previous smokers (**Table 1**). As observed in the general population at the time, more men smoked (84%) than women (55%, p<0.001, **Table 4**). Based on an age or date of stopping smoking obtained for all previous smokers, the median duration of smoking cessation was 16 years (mean 18.8 years). In univariate analysis there was a trend for cigarette smoking to be associated with increased cumulative incidence of death due to UBC, death from other cancers, and death from other causes, but none reached significance (Supplementary Figure 1a).

Occupational Carcinogen Exposure

We identified that 27% of patients had worked in occupations linked with UBC, with higher exposure in males (31%) than females (14%, $p<0.0001$, **Table 3**). There was a trend for occupational exposure to be associated with increased cumulative incidence of death due to UBC and death due to other causes, but none reached significance (Supplementary Figure 1b).

Pathway delays

The median time from initial onset of symptoms to GP referral was 14days (Time 1, IQR: 0-61), from referral to hospital consultation was 28days (Time 2, IQR: 7-61), and from consultation to first treatment was 20days (Time 3, IQR: 0-50). Patient characteristics by delay times are shown in **Table 4**. Longer delays in Time 3 and Hospital Delay were associated with smaller tumour size ($p<0.05$ for both). A longer Total Delay was seen for females (120days vs. 106days, $p<0.05$) and non-smokers (118days vs. 105days, $p<0.05$) when compared to other patients.

Analysis of survival by delay stratified for tumour stage demonstrated no impact (Supplementary Table 2), except for patients with MIBC for whom a shorter delay Time 3 resulted in worse survival compared to those with longer delay ($p<0.05$).

Predictors of Survival

Univariate analysis identified histopathological criteria, gender, delays and smoking as factors associated with UBC outcomes. Since these parameters are not necessarily

independent, multivariate analysis was used to determine the impact of each feature. Cox regression of delay times adjusted by a base model of independent factors identified that age, smoking status, and tumour stage (MIBC), grade (3), and size (>2cm) were the most significant determinants of poor outcome from UBC (Supplementary Table 3). There was no significant influence of delay, gender or occupational exposure.

DISCUSSION

Here we report 17-year outcomes from newly-diagnosed cases of UBC within a large geographic region in the UK. We have updated an initial report [9], and now have most cases (75%) followed until death. We are thus able to examine the complex interaction between the tumour, patient gender, carcinogen exposures, pathway delays, and mortality. We identified in univariate and competing risks analysis that many of these factors were associated with disease-specific mortality. However, multivariate analysis identified age, smoking status, and tumour stage, grade, and size as the most significant determinants of poor outcome from UBC. Notably, there was no significant influence of delay, gender or occupational exposure.

Comparison of CIFs demonstrated significant associations between female gender and higher cumulative incidence of death from grade 3 disease and MIBC, concurring with previous reports of worse outcomes for females with UBC [1;16;17;23;24]. Furthermore, there was a trend for female patients to present more commonly with MIBC than male patients. Importantly, female patients experienced a significantly longer Total Delay than male patients. The majority of this delay occurred in Time 1, before referral for investigation in secondary care was implemented by GPs; a significantly higher proportion of female patients with visible haematuria encountered longer delays in Time 1 than equivalent male patients. These data support observations of repeated community-based treatments for suspected urinary infection in symptomatic females [25;26]. As reported by Hollenbeck et al. [7], there were no significant differences in delays between the genders once patients were within secondary care.

Female patients with MIBC had a significantly higher cumulative incidence of death from UBC than male patients; it is unlikely that differential utilisation of radiotherapy or cystectomy between the genders would cause this effect, but there is limited evidence to suggest that female patients have worse outcomes from radiotherapy compared to males [27]. However, such effects were not large enough for gender to be an independent prognostic factor in multivariate analysis when adjusted for pathway delays.

It is a commonly-held belief that more rapid cancer diagnosis and treatment leads to better outcomes, and to suggest otherwise is counterintuitive [5;6]. However, the relationship between delay and survival in UBC is complex [8;9], with no direct linear relationship with any components of delay [6;9]. In the long-term follow-up of this cohort, we have confirmed this complex relationship, as noted by others [6;8;9]: no delay category had a significant influence on survival, except for patients with MIBC for whom a shorter Delay 3 was detrimental. This may represent an anomaly, and there is no clear explanation from our data, but it is feasible that patients with MIBCs with concerning features (e.g. ongoing bleeding) or comorbidities were selected for expedited treatment [9], subsequently succumbing more rapidly as a result of those features or comorbidities. This was also postulated by Liedberg, who demonstrated that a long treatment delay had no influence on survival following cystectomy [8]. Seemingly, once in secondary care, clinicians are good at selecting the highest risk patients and treating them rapidly [9]. Similarly, Nielsen demonstrated that delay from TURBT to radical cystectomy was not independently associated with stage progression or decreased recurrence-free or disease-specific survival [28]. Likewise, for UBC patients treated by radiotherapy, there is no significant influence of

277 treatment delay on survival [29]. However, Hollenbeck investigated delay and survival in
278 29,826 patients with UBC and demonstrated that longer delays from presentation to
279 diagnosis were associated with increased risk of bladder cancer-specific mortality [7], a
280 finding also demonstrated by Gore when assessing the interval between TURBT and
281 cystectomy [30].
282
283 Many patient-related factors analysed here are not independent, e.g. males are more likely
284 to smoke, to have occupational carcinogen exposure, and to be more rapidly referred for
285 the investigation of haematuria [15]. Females are more likely to be non-smokers, are
286 typically exposed to different occupational carcinogens, and are slower to be referred for
287 investigation of haematuria or lower urinary tract symptoms [15;25;26]. In multivariate
288 analysis, we identified that only tumour stage, grade and size, and patient age and smoking
289 exposure were predictors of outcome when adjusted for pathway delays. These reinforce
290 observations from RCTs of bladder cancer treatment, and suggest that gender-related
291 disparities arise at least partly from a disease stage/grade migration due to diagnostic delay.
292
293 A major limitation of this study is a lack of delay data 'downstream' from TURBT. However,
294 the classification and interpretation of such data could be challenging (e.g. classifying the
295 time to definitive treatment of MIBC in the setting of chemoradiotherapy or neoadjuvant
296 chemotherapy/cystectomy), whereas TURBT remains the first intervention for all cases of
297 UBC [11;12]. It could also be suggested that our outcome data are not applicable to modern
298 practice (although outcomes from UBC have remained unchanged for over 30 years [3]), for
299 example, there appear to be high rates of UBC-specific death for patients with Ta and T1

tumours; in 1991 these patients may have been understaged and undertreated in an era when re-TUR was rare and the utilisation of intravesical therapies was uncommon. Furthermore, disease surveillance was according to national guidelines and may have limited generalisability for other healthcare systems. Given the nature of multicentre cohort studies, there was also likely to be heterogeneity in both treatment and surveillance strategies between participating units. Finally, the gathering of more comprehensive smoking and occupation data would have been more illuminating than the limited categorical data presented here. The strengths of this study include its prospective nature, its mature and long-term follow-up, and the completeness of data from a large cohort.

CONCLUSIONS

Our data demonstrate a stage migration to MIBC in female patients at presentation. The relationships between gender, outcomes, delays and aetiology of UBC are complex. Female patients experience a significantly longer Total Delay than male patients, the majority of which results from a delay in referral from general practice to secondary care/urological assessment, and may contribute to stage migration. GPs should be particularly vigilant regarding symptoms that are associated with UBC, and especially in female patients; visible haematuria always requires urgent referral to secondary care for urological assessment.

LEGENDS FOR TABLES AND FIGURES

Table 1: Overall patient and tumour characteristics (where recorded).

Table 2: Certified causes of death by tumour stage in the 983 patients where both tumour stage and cause of death were known.

Table 3: Gender-specific characteristics of patients in the cohort.

Table 4: Patient characteristics by delay times (in days), *n* (%). VH=visible hameaturia; NVH=non-visible haematuria.

Figure 1: Survival by tumour stage and estimated survival for the general population.

Figure 2a: Cumulative incidence of death due to bladder cancer, other cancer and other causes by gender and tumour stage (solid lines=male patients, dashed lines=female patients).

Figure 2b: Cumulative incidence of death due to bladder cancer, other cancer and other causes by gender and tumour grade (solid lines=male patients, dashed lines=female patients).

345 **Table 1:** Overall patient and tumour characteristics (where recorded).

Variable	Number (%)
Gender (1478 responses, 100%)	
Male	1097 (74)
Female	381 (26)
Haematuria at presentation (1171 responses, 79%)	
Visible	1021 (87)
Non-visible	67 (6)
None	83 (7)
Age, years (1478 responses, 100%)	
<60	315 (21)
61-70	478 (32)
71-80	495 (33)
>80	190 (13)
Smoking history (1260 responses, 85%)	
Current smoker	330 (26)
Previous smoker	643 (51)
Never smoked	287 (23)
Occupational exposure (1240 responses, 84%)	
Known or suspected increased relative risk	330 (27)
No increased relative risk	910 (73)
Tumour type (1404 responses, 95%)	
Papillary	903 (64)
Solid	246 (18)
Mixed	255 (18)
Tumour number (1392 responses, 94%)	
Single	1042 (75)
2 or more	350 (25)
Tumour size, cm (1366 responses, 92%)	
≤2	552 (40)
>2	814 (60)
Tumour stage (1300 responses, 88%)	
pTa	658 (51)
pT1	291 (22)
T2-T4	351 (27)
Grade (1347 responses, 91%)	
Well (G1)	475 (35)
Moderate (G2)	513 (38)
Poor and anaplastic (G3)	359 (27)

346 **Table 2:** Certified causes of death by tumour stage in the 983 patients where both tumour stage and cause of death were known.

Cause	**pTa** (%)*					**pT1** (%)*					**T2-T4** (%)*	Total
	Well (G1)	Moderate (G2)	Poor and anaplastic (G3)	Unknown	All grades	Well (G1)	Moderate (G2)	Poor and anaplastic (G3)	Unknown	All grades	All grades	
Bladder Cancer	31 (12)	30 (19)	5 (36)	1 (09)	67 (15)	11 (38)	39 (34)	24 (35)	5 (42)	79 (35)	219 (69)	365
Other Cancer	65 (25)	31 (20)	2 (14)	2 (18)	100 (23)	5 (17)	12 (11)	10 (14)	2 (17)	29 (13)	24 (8)	153
Other Causes	165 (63)	94 (61)	7 (50)	8 (73)	274 (62)	13 (45)	63 (55)	35 (51)	5 (42)	116 (52)	75 (24)	465
Total	261	155	14	11	441	29	114	69	12	224	318	983

*Rounded proportions may sum to more than 100%

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Table 3: Gender-specific characteristics of patients in the cohort.

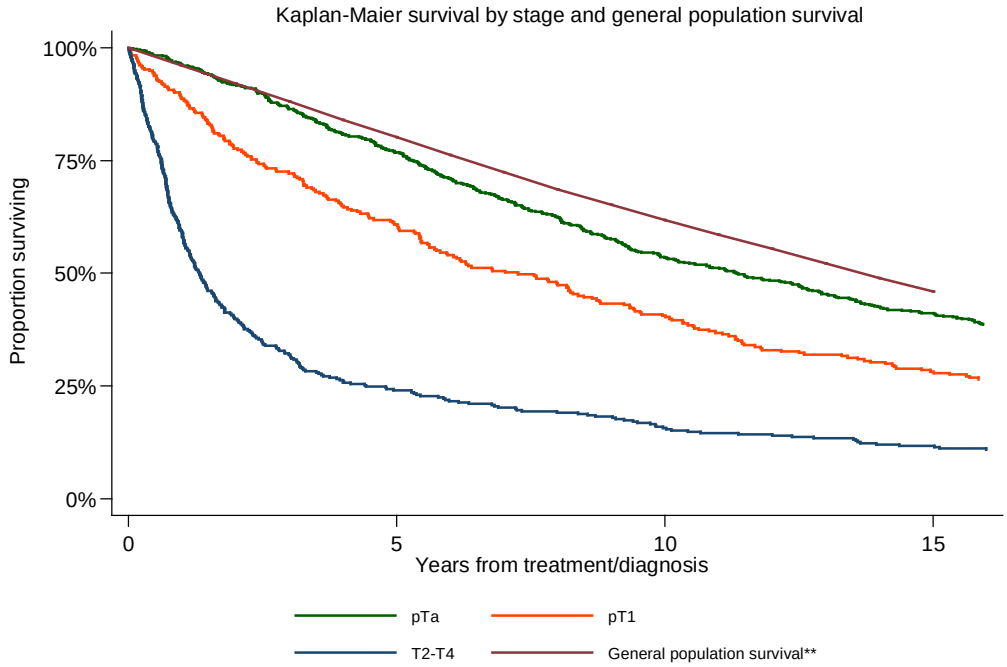
	Males	Females	p
Proportions	74%	26%	<0.001
Haematuria at presentation			
Visible	87%	89%	0.673
Non-visible	6%	5%	
None	7%	6%	
Grade			
G1	34%	39%	0.157
G2	39%	35%	
G3	27%	26%	
Stage			
Ta	50%	52%	0.060
T1	24%	18%	
T2-4	26%	30%	
Median Delay Time 1	14	23	0.101
Delay 1 ≤14 days	51%	46%	
Delay 1 >14 days	49%	54%	
Median Delay Time 2	27	29	0.498
Delay 2 ≤28 days	52%	50%	
Delay 2 >28 days	48%	50%	
Median Delay Time 3	22	18	0.152
Delay 3 ≤20 days	48%	52%	
Delay 3 >20 days	52%	48%	
Median Hospital Delay	68	68	0.848
Hospital Delay ≤68 days	51%	51%	
Hospital Delay >68 days	49%	49%	
Median Total Delay	106	120	0.024
Total Delay ≤110 days	52%	45%	
Total Delay >110 days	48%	55%	
History of smoking	84%	55%	<0.001
History of occupational exposure	31%	14%	<0.001

Table 4: Patient characteristics by delay times (in days), *n* (%).

			Time 1: Initial symptom to GP referral		Time 2: GP referral to first consultation		Time 3: Consultation to first Treatment		Hospital Delay		Total Delay	
Factor	Grouping	N	≤14	>14	≤28	>28	≤20	>20	≤68	>68	≤110	>110
Median age, years			70	69	69	70	70	69	70	69	69	70
IQR			62-77	61-76	61-76	62-77	62-77	62-76	62-76	62-76	62-76	62-76
Sex	Male	1097	548 (76)	523 (72)	553 (75)	518 (73)	511 (73)	560 (76)	549 (74)	525 (74)	558 (77)*	513 (72)*
	Female	381	171 (24)	199 (28)	184 (25)	187 (27)	193 (27)	178 (24)	188 (26)	184 (26)	168 (23)	203 (28)
Tumour stage	pTa	658	340 (54)	314 (48)	345 (52)	309 (50)	312 (51)	342 (51)	321 (49)	333 (52)	320 (50)	334 (52)
	pT1	291	140 (22)	149 (23)	140 (21)	149 (24)	131 (21)	158 (24)	148 (23)	142 (22)	146 (23)	143 (22)
	T2-T4	351	154 (24)	186 (29)	176 (27)	164 (26)	168 (27)	172 (26)	181 (28)	161 (25)	179 (28)	161 (25)
Tumour size, cm	≤2	552	286 (42)	259 (38)	272 (39)	274 (41)	244 (37)	302 (43)	247 (36)	301 (45)	259 (38)	287 (42)
	>2	814	388 (58)	419 (62)	417 (61)	390 (59)	412 (63)*	395 (57)*	439 (64)*	370 (55)*	417 (62)	390 (58)
Presenting with haematuria	VH (M)	755	301 (78)*	445 (72)*	452 (75)	149 (73)	259 (73)	487 (75)	405 (73)	343 (75)	390 (76)	356 (72)
	VH (F)	266	86 (22)	174 (28)	149 (25)	111 (27)	98 (27)	162 (25)	148 (27)	113 (25)	124 (24)	136 (28)
	NVH (M)	52	26 (79)	25 (76)	22 (76)	29 (78)	16 (76)	35 (78)	26 (76)	25 (78)	23 (74)	28 (80)
	NVH (F)	15	7 (21)	8 (24)	7 (24)	8 (22)	5 (24)	10 (22)	8 (24)	7 (22)	8 (26)	7 (20)
	None (M)	64	28 (82)	35 (73)	34 (69)	29 (88)	28 (65)	35 (90)	33 (73)	31 (82)	29 (74)	34 (79)
	None (F)	19	6 (18)	13 (27)	15 (31)	4 (12)	15 (35)*	4 (10)*	12 (27)	7 (18)	10 (26)	9 (21)
Smoking	Never	287	133 (21)	147 (24)	142 (22)	138 (23)	140 (23)	140 (22)	138 (22)	142 (23)	126 (20)	154 (25)
	Ever	973	486 (79)	471 (76)	490 (78)	467 (77)	459 (77)	498 (78)	492 (78)	467 (77)	500 (80)*	457 (75)*

**P<0.05*

Figure 1: Survival by tumour stage and estimated survival for the general population.



** General population survival for pTa tumours, matched by year of diagnosis, sex and age

Figure 2a: Cumulative incidence of death due to bladder cancer, other cancer and other causes by gender and tumour stage (solid lines=male patients, dash lines=female patients).

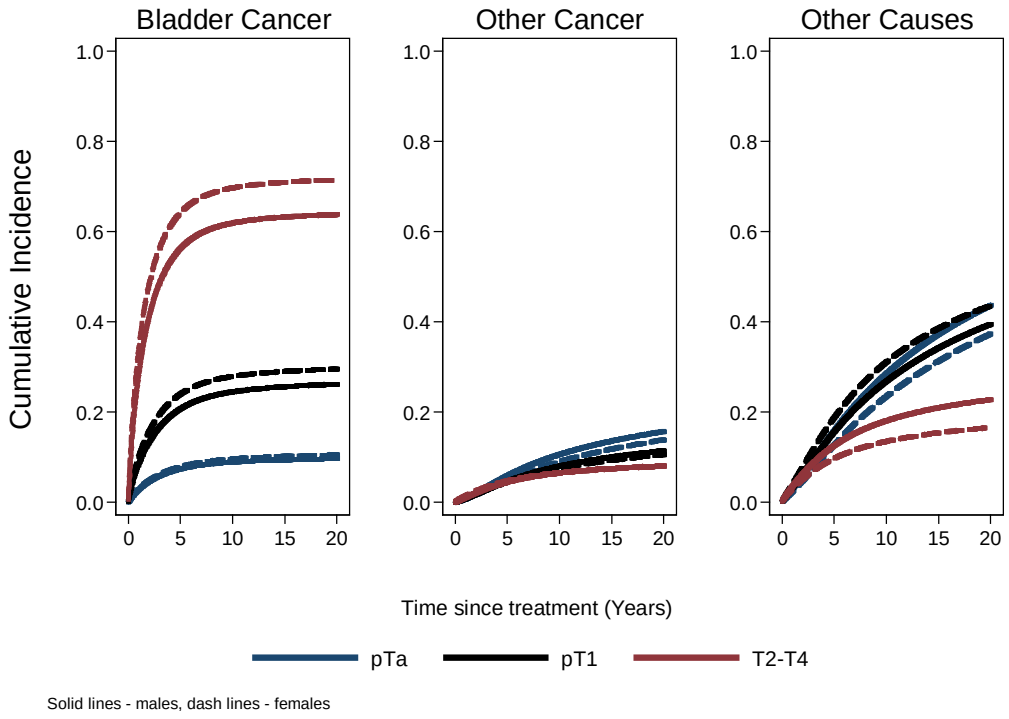
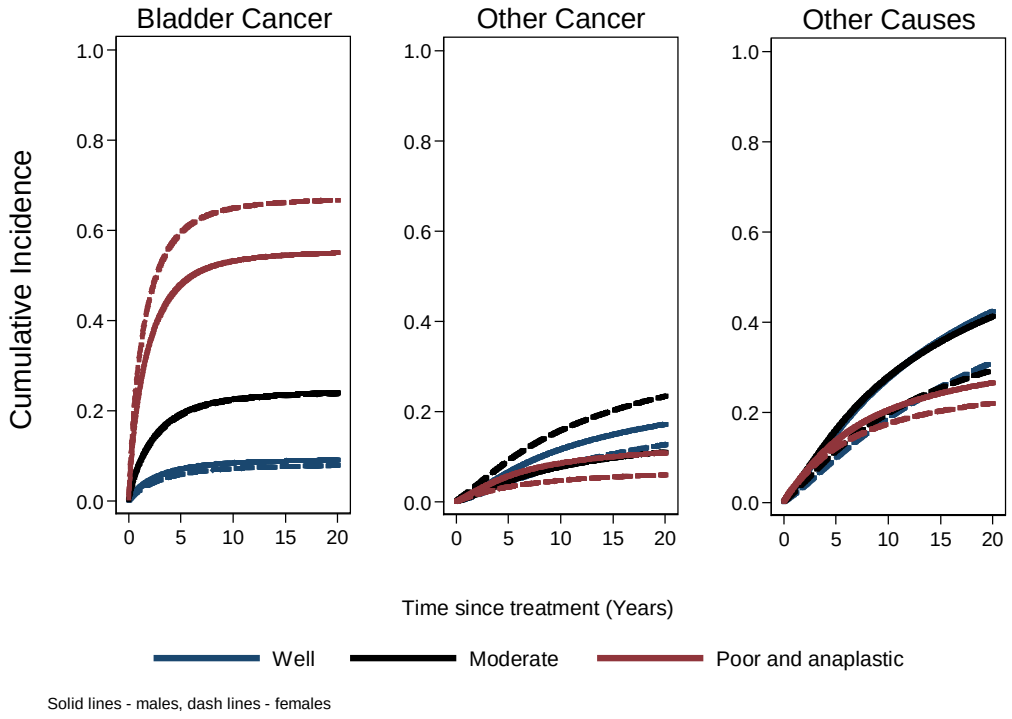


Figure 2b: Cumulative incidence of death due to bladder cancer, other cancer and other causes by gender and tumour grade (solid lines=male patients, dashed lines=female patients).



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A COMPARATIVE ANALYSIS OF GENDER, PATHWAY DELAYS AND RISK FACTOR EXPOSURES ON THE LONG-TERM OUTCOMES FROM BLADDER CANCER

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SUPPLEMENTARY METHODS & DATA

SUPPLEMENTARY METHODS

To assess the competing risks of death in our cohort, we first used a non-parametric test to assess the equality between groups by calculating the cumulative incidence function (CIF) as described by Scrucca et al. [1]. Comparison of specific CIFs was performed using Gray's test [2]. We then extended our analysis to investigate the effects of other covariates (stage at diagnosis, tumour grade, gender, smoking status, occupational exposure risk and age group at diagnosis), present in our data on the CIF. We constructed flexible parametric models using the user written Stata command stpm2 in order to calculate the cause-specific hazard for each cause and for each covariate of interest [3]. Gender and cause of death were modeled as time-varying covariates. We used information from the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for model selection. Post-estimation we applied the user written stpm2cif command [4], so that the cumulative incidence function for each model of interest could be derived and graphed.

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LEGENDS

Supplementary Table 1: Occupations with known or suspected exposure to urothelial carcinogens, and chemicals implicated in urothelial carcinogenesis. These data were utilised by the assessors to assign risk of occupational exposure.

Supplementary Table 2: Survival by delay times stratified for tumour stage.

Supplementary Table 3: Cox regression of delay times adjusted by a base model of independent factors.

Supplementary Figure 1a: Cumulative incidence of death due to bladder cancer, other cancer and other causes by smoking status (blue line=non-smoker, red line=current or ex-smoker).

Supplementary Figure 1b: Cumulative incidence of death due to bladder cancer, other cancer and other causes by risk of occupational exposure to bladder carcinogens (blue line=known or suspected risk of occupational exposure, red line=no increased risk of occupational exposure).

Supplementary Table 1: Occupations and carcinogens associated with urothelial carcinogenesis.

Occupations with exposure to urothelial carcinogens	Occupations with suspicion of an excess of bladder cancer	Implicated chemicals
Manufacture of rubber & rubber products	Leather working	1-Naphthylamine
Cable manufacturing industry	Manufacture and use of paint	2-Naphthylamine
Manufacture of dyestuffs	Plastics industry	3,3'-Dicholorbenzidine
Manufacture of organic chemicals	Medical and nursing	3,3'-Dicholorbenzidine hydrochloride
Gasworks, coke oven and iron foundry working	Textile printing and dyeing	3,3'-Dimethoxybenzidine (o-Dianisidine)
Rodent extermination	Hairdressing	3,3'-Dimethylbenzidine (o-Tolidine)
Sewage works	Aluminium refining and smelting	4,4'-Methylene bis (2-Chloroaniline)
Manufacture of firelighters/patent fuels	Security printing	4,4'-Methylenedianiline (MDA)
Laboratory work	Mechanics and land transport working	4-Aminobiphenyl
	Machine turning	4-Chloro-o-toluidine (4-COT)
		Aniline
		Auramine
		Benzidine
		Benzidine dihydrochloride
		Benzidine hydrochloride
		Benzidine sulphate
		Magenta
		Phenyl 1-naphthylamine
		Phenyl b-naphthylamine

Supplementary Table 2: Survival by delay times stratified for tumour stage.

DELAY, N DAYS	N	Dead (N)	%Alive	O/E	Median [95% CI] survival, years		Surviving at years 1	3	5	10
Time 1 (P=0.09)										
≤14	719	524	27.1%	0.97	7.8	[6.7,8.7]	86%	70%	61%	42%
>14	722	554	23.3%	1.03	6.4	[5.6,7.5]	83%	67%	58%	39%
Time 1 by tumour stage (P=<0.001)										
pTa										
≤14	340	220	35.3%	0.86	11.8	[9.5,13.4]	97%	87%	78%	55%
>14	314	212	32.5%	0.90	10.8	[9.1,12.6]	96%	86%	75%	52%
pT1										
≤14	140	102	27.1%	0.97	8.0	[6.1,10.4]	90%	76%	65%	42%
>14	149	120	19.5%	1.08	5.7	[4.8,9.3]	88%	69%	58%	40%
T2-T4										
≤14	154	140	9.1%	1.21	1.3	[1.0,1.7]	58%	31%	23%	15%
>14	186	166	10.8%	1.19	1.3	[1.0,1.6]	59%	33%	25%	17%
Time 2 (P=0.09)										
≤28	737	565	23.3%	1.03	6.2	[5.4,7.4]	83%	66%	57%	38%
>28	705	513	27.2%	0.97	8.2	[7.0,9.0]	86%	71%	62%	43%
Time 2 by tumour stage (P=<0.001)										
pTa										
≤28	345	238	31.0%	0.92	9.6	[8.6,11.5]	97%	85%	75%	49%
>28	309	194	37.2%	0.84	12.9	[11.1,15.1]	96%	88%	79%	59%
pT1										
≤28	140	109	22.1%	1.04	6.2	[4.4,10.0]	87%	70%	57%	42%
>28	149	113	24.2%	1.01	7.8	[5.8,9.3]	91%	75%	65%	40%

T2-T4										
≤28	176	160	9.1%	1.21	1.1	[0.9,1.5]	55%	30%	21%	14%
>28	164	146	11.0%	1.19	1.4	[1.1,2.1]	63%	34%	27%	18%
Time 3 (P=0.45)										
≤20	704	520	26.1%	0.99	6.8	[5.5,8.1]	82%	66%	56%	39%
>20	738	558	24.4%	1.01	7.5	[6.4,8.4]	87%	71%	62%	42%
Time 3 by tumour stage (P=<0.001)										
pTa										
≤20	312	208	33.3%	0.89	10.1	[9.0,12.8]	95%	84%	73%	51%
>20	342	224	34.5%	0.88	12.1	[10.0,13.4]	98%	89%	80%	56%
pT1										
≤20	131	90	31.3%	0.92	8.8	[5.8,11.4]	90%	76%	63%	47%
>20	158	132	16.5%	1.12	6.2	[5.0,8.2]	88%	70%	59%	35%
T2-T4										
≤20	168	155	7.7%	1.23	1.0	[0.8,1.2]	53%	26%	18%	12%
>20	172	151	12.2%	1.17	1.8	[1.3,2.4]	65%	38%	30%	20%
Hospital Delay (P=0.30)										
≤68	737	560	24.0%	1.02	6.1	[5.4,7.4]	82%	65%	56%	37%
>68	709	522	26.4%	0.98	8.1	[6.8,8.9]	87%	72%	62%	43%
Hospital Delay by tumour stage (P=<0.001)										
pTa										
≤68	321	221	31.2%	0.92	9.6	[8.4,11.6]	96%	84%	74%	49%
>68	333	211	36.6%	0.85	12.9	[11.1,14.1]	97%	89%	79%	58%
pT1										
≤68	148	112	24.3%	1.01	7.8	[5.0,10.0]	87%	72%	59%	43%
>68	142	111	21.8%	1.04	7.0	[5.6,8.6]	90%	73%	63%	39%
T2-T4										
≤68	181	160	11.6%	1.18	1.1	[0.9,1.3]	55%	30%	23%	17%

>68	161	148	8.1%	1.23	1.7	[1.2,2.1]	64%	34%	26%	16%
Total Delay (P=0.26)										
≤110	726	552	24.0%	1.02	6.9	[5.6,7.9]	83%	66%	58%	39%
>110	716	526	26.5%	0.98	7.4	[6.4,8.6]	86%	71%	60%	41%
Total Delay by tumour stage (P=<0.001)										
pTa										
≤110	320	217	32.2%	0.91	10.5	[9.0,12.3]	96%	86%	76%	52%
>110	334	215	35.6%	0.86	12.5	[9.9,14.4]	96%	87%	78%	55%
pT1										
≤110	146	112	23.3%	1.03	8.4	[6.2,10.5]	88%	74%	66%	46%
>110	143	110	23.1%	1.03	5.7	[4.4,8.2]	90%	71%	57%	36%
T2-T4										
≤110	179	160	10.6%	1.19	1.1	[0.8,1.4]	54%	30%	22%	16%
>110	161	146	9.3%	1.21	1.6	[1.2,2.1]	64%	34%	26%	16%

Supplementary Table 3: Cox regression of delay times adjusted by a base model of independent factors.

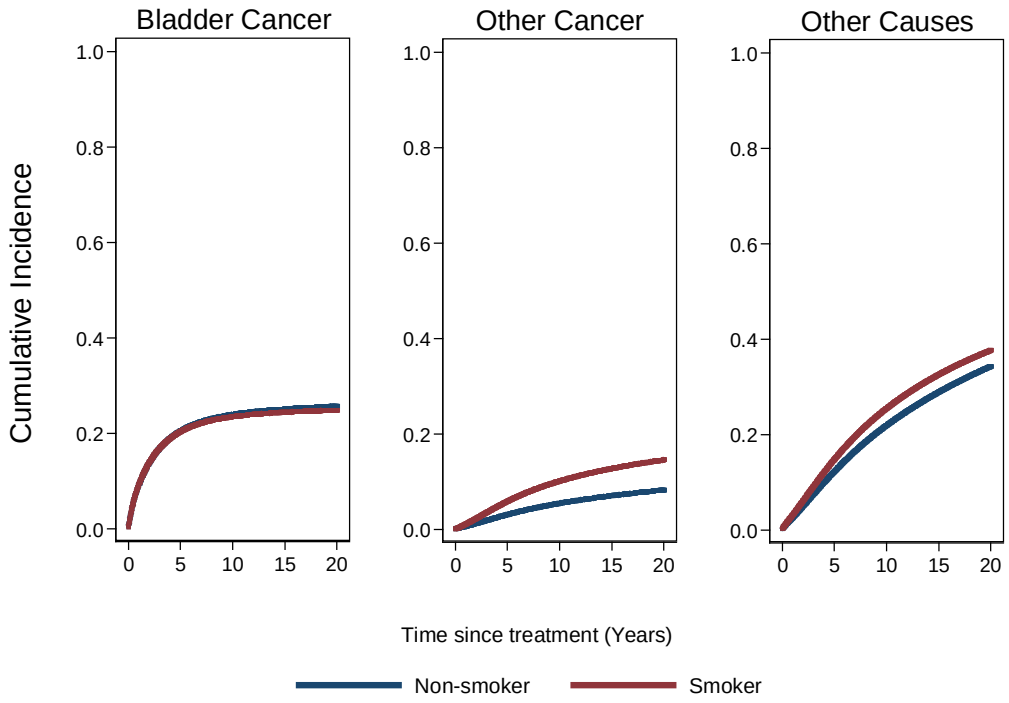
Factor	Grouping	Coefficient	z	P	Hazard ratio (95% CI)
Time 1 adjusted by base model (n=1001)					
Time 1	(≤14, >14 days)	0.10	1.34	0.18	1.11 (0.95,1.28)
Age	(Continous)	0.06	13.98	<0.001	1.06 (1.05,1.07)
Tumour type					
	(Papilliary)				1 (1,1)
	(Mixed)	0.24	1.67	0.09	1.27 (0.96,1.67)
	(Solid)	0.13	1.11	0.27	1.14 (0.91,1.43)
Tumour stage					
	(pTa)				1 (1,1)
	(pT1)	0.10	0.95	0.34	1.11 (0.90,1.36)
	(T2-T4)	0.50	3.43	<0.001	1.65 (1.24,2.20)
Smoking	*(Never, ever)*	0.36	3.72	<0.001	1.44 (1.19,1.74)
Occupational exposure	*(No increased risk, known or suspect risk)*	0.06	0.70	0.48	1.06 (0.90,1.26)
Sex	*(Female, Male)*	0.02	0.16	0.87	1.02 (0.84,1.22)
Tumour grade					
	(Well differentiated)				1 (1,1)
	(Moderately differentiated)	0.02	0.23	0.82	1.02 (0.85,1.23)
	(Poorly differentiated)	0.31	2.26	0.02	1.36 (1.04,1.77)
Tumour size (cm)	(≤2, >2)	0.15	1.90	0.06	1.17 (0.99,1.36)
Time 2 adjusted by base model (n=1001)					
Time 2	(≤28, >28 days)	-0.11	-1.44	0.15	0.90 (0.78,1.04)
Age	(Continous)	0.06	13.89	<0.001	1.06 (1.05,1.07)
Tumour type					
	(Papilliary)				1 (1,1)
	(Mixed)	0.24	1.72	0.09	1.27 (0.97,1.68)
	(Solid)	0.13	1.11	0.27	1.14 (0.90,1.43)

Tumour stage					
	(pTa)				1 (1,1)
	(pT1)	0.11	1.03	0.31	1.11 (0.91,1.37)
	(T2-T4)	0.52	3.58	<0.001	1.69 (1.27,2.24)
Smoking	*(Never, ever)*	0.36	3.69	<0.001	1.44 (1.19,1.74)
Occupational exposure	*(No increased risk, known or suspect risk)*	0.05	0.58	0.56	1.05 (0.89,1.24)
Sex	*(Female, Male)*	0.01	0.10	0.92	1.01 (0.84,1.21)
Tumour grade					
	(Well differentiated)				1 (1,1)
	(Moderately differentiated)	0.02	0.22	0.82	1.02 (0.85,1.23)
	(Poorly differentiated)	0.30	2.24	0.03	1.35 (1.04,1.76)
Tumour size (cm)	(≤2, >2)	0.15	1.89	0.06	1.16 (0.99,1.36)
Time 3 adjusted by base model (n=1001)					
Time 3	(≤20, >20 days)	-0.09	-1.15	0.25	0.92 (0.79,1.06)
Age	(Continous)	0.06	13.91	<0.001	1.06 (1.05,1.07)
Tumour type					
	(Papilliary)				1 (1,1)
	(Mixed)	0.24	1.71	0.09	1.27 (0.96,1.68)
	(Solid)	0.13	1.11	0.27	1.14 (0.91,1.43)
Tumour stage					
	(pTa)				1 (1,1)
	(pT1)	0.10	1.00	0.32	1.11 (0.90,1.36)
	(T2-T4)	0.51	3.50	<0.001	1.66 (1.25,2.21)
Smoking	*(Never, ever)*	0.37	3.73	<0.001	1.44 (1.19,1.75)
Occupational exposure	*(No increased risk, known or suspect risk)*	0.06	0.69	0.49	1.06 (0.90,1.25)
Sex	*(Female, Male)*	0.01	0.09	0.93	1.01 (0.84,1.21)
Tumour grade					
	(Well differentiated)				1 (1,1)
	(Moderately differentiated)	0.01	0.13	0.89	1.01 (0.84,1.22)

	(Poorly differentiated)	0.32	2.35	0.02	1.37 (1.05,1.79)
Tumour size (cm)	(≤2, >2)	0.15	1.87	0.06	1.16 (0.99,1.36)
Hospital delay adjusted by base model (n=1003)					
Hospital delay	(≤68, >68 days)	-0.06	-0.84	0.40	0.94 (0.81,1.09)
Age	(Continous)	0.06	13.95	<0.001	1.06 (1.05,1.07)
Tumour type					
	(Papilliary)				1 (1,1)
	(Mixed)	0.24	1.68	0.09	1.27 (0.96,1.67)
	(Solid)	0.13	1.09	0.28	1.14 (0.90,1.43)
Tumour stage					
	(pTa)				1 (1,1)
	(pT1)	0.11	1.04	0.3	1.12 (0.91,1.37)
	(T2-T4)	0.51	3.50	<0.001	1.66 (1.25,2.21)
Smoking	*(Never, ever)*	0.37	3.73	<0.001	1.44 (1.19,1.75)
Occupational exposure	*(No increased risk, known or suspect risk)*	0.06	0.66	0.51	1.06 (0.89,1.25)
Sex	*(Female, Male)*	0.01	0.14	0.89	1.01 (0.84,1.22)
Tumour grade					
	(Well differentiated)				1 (1,1)
	(Moderately differentiated)	0.02	0.21	0.83	1.02 (0.85,1.23)
	(Poorly differentiated)	0.32	2.35	0.02	1.37 (1.05,1.79)
Tumour size (cm)	(≤2, >2)	0.14	1.77	0.08	1.15 (0.98,1.35)
Total delay adjusted by base model (n=1001)					
Total delay	(≤110, >110 days)	0.01	0.18	0.86	1.01 (0.88,1.17)
Age	(Continous)	0.06	13.92	<0.001	1.06 (1.05,1.07)
Tumour type					
	(Papilliary)				1 (1,1)
	(Mixed)	0.24	1.70	0.09	1.27 (0.96,1.68)
	(Solid)	0.13	1.09	0.28	1.14 (0.90,1.43)
Tumour stage					

	(pTa)			<0.001	1 (1,1)
	(pT1)	0.11	1.02	0.31	1.11 (0.91,1.37)
	(T2-T4)	0.51	3.46	<0.001	1.66 (1.25,2.21)
Smoking	*(Never, ever)*	0.37	3.73	<0.001	1.44 (1.19,1.75)
Occupational exposure	*(No increased risk, known or suspect risk)*	0.06	0.70	0.48	1.06 (0.90,1.26)
Sex	*(Female, Male)*	0.01	0.12	0.91	1.01 (0.84,1.22)
Tumour grade					
	(Well differentiated)				1 (1,1)
	(Moderately differentiated)	0.02	0.19	0.85	1.02 (0.85,1.23)
	(Poorly differentiated)	0.31	2.29	0.02	1.36 (1.05,1.78)
Tumour size (cm)	(≤2, >2)	0.16	1.92	0.05	1.17 (1.00,1.37)

Supplementary Figure 1a: Cumulative incidence of death due to bladder cancer, other cancer and other causes by smoking status (blue line=non-smoker, red line=current or ex-smoker).



Supplementary Figure 1b: Cumulative incidence of death due to bladder cancer, other cancer and other causes by risk of occupational exposure to bladder carcinogens (blue line=known or suspected risk of occupational exposure, red line=no increased risk of occupational exposure).